

REVIEW

## Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis

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### WHAT THIS PAPER ADDS

This meta-analysis of prospective surveillance data derived from nine randomised controlled trials found that CAS patients with an untreated asymptomatic > 70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 50 months). CEA patients with an untreated, asymptomatic > 70% restenosis had a significantly higher risk of late ipsilateral stroke (compared with patients with no restenosis), but the risk was only 5% at 37 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients with no evidence of a significant restenosis or occlusion.

**Objective:** Do asymptomatic restenoses > 70% after carotid endarterectomy (CEA) and carotid stenting (CAS) increase the risk of late ipsilateral stroke?

**Methods:** Systematic review identified 11 randomised controlled trials (RCTs) reporting rates of restenosis > 70% (and/or occlusion) in patients who had undergone CEA/CAS for the treatment of primary atherosclerotic disease, and nine RCTs reported late ipsilateral stroke rates. Proportional meta-analyses and odds ratios (OR) at end of follow-up were performed.

**Results:** The weighted incidence of restenosis > 70% was 5.8% after “any” CEA, median 47 months (11 RCTs; 4249 patients); 4.1% after patched CEA, median 32 months (5 RCTs; 1078 patients), and 10% after CAS, median 62 months (5 RCTs; 2716 patients). In four RCTs (1964 patients), one of 125 (0.8%) with restenosis > 70% (or occlusion) after CAS suffered late ipsilateral stroke over a median 50 months, compared with 37 of 1839 (2.0%) in CAS patients with no significant restenosis (OR 0.87; 95% CI 0.24–3.21;  $p = .8339$ ). In seven RCTs (2810 patients), 13 out of 141 (9.2%) with restenosis > 70% (or occlusion) after CEA suffered late ipsilateral stroke over a median 37 months, compared with 33 out of 2669 (1.2%) in patients with no significant restenoses (OR 9.02; 95% CI 4.70–17.28;  $p < .0001$ ). Following data correction to exclude patients whose surveillance scan showed no evidence of restenosis > 70% before stroke onset, the prevalence of stroke ipsilateral to an untreated asymptomatic > 70% restenosis was seven out of 135 (5.2%) versus 40 out of 2704 (1.5%) in CEA patients with no significant restenosis (OR 4.77; 95% CI 2.29–9.92).

**Conclusions:** CAS patients with untreated asymptomatic > 70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 50 months). CEA patients with untreated, asymptomatic > 70% restenosis had a significantly higher risk of late ipsilateral stroke (compared with patients with no restenosis), but this was only 5% at 37 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients without evidence of significant restenosis or occlusion.

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Article history: Received 26 October 2016, Accepted 13 February 2017, Available online 28 March 2017

**Keywords:** Carotid endarterectomy, Carotid stenting, Restenosis, Recurrent stroke

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<http://dx.doi.org/10.1016/j.ejvs.2017.02.016>

### INTRODUCTION

In a 1997 systematic review, up to 8% of patients undergoing carotid endarterectomy (CEA) developed a significant restenosis of the operated internal carotid artery (ICA)

during follow-up.<sup>1</sup> However, very few (if any) contemporary practice guidelines provide specific advice on how these patients should be managed, especially as most are asymptomatic at the point of detection after CEA or carotid artery stenting (CAS). The 2011 '14-Society' Guidelines on the management of extracranial carotid artery disease commented that "restenosis is generally benign and does not require revascularisation, except when it leads to recurrent ischaemic symptoms or progresses to pre-occlusive severity. Under these circumstances, it may be justifiable to repeat revascularisation, either by CEA in the hands of an experienced surgeon or by CAS".<sup>2</sup> However, this "comment" was never promoted to become a formal recommendation and surgeons/interventionists have been left to manage patients on a case by case basis. No-one would dispute that most patients with a symptomatic restenosis > 50% warrant re-intervention (unless contraindicated), but what about patients with asymptomatic 70–99% restenoses? Despite the informal advice provided by the 14-Society Guidelines, meta-analyses of contemporary practice suggest that two thirds of patients undergoing re-interventions for restenoses after CEA are asymptomatic,<sup>3</sup> suggesting that many surgeons and interventionists remain uncomfortable about not re-intervening.

Data from individual multicentre randomised controlled trials (RCTs) have provided conflicting evidence of whether restenoses after CEA/CAS are associated with an increased risk of recurrent ipsilateral stroke. Some have reported no statistically significant association between restenosis and recurrent ipsilateral stroke<sup>4–6</sup>; the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) reported that restenoses > 70% after CEA were associated with a significantly higher prevalence of recurrent stroke after CEA, but not after CAS.<sup>7</sup>

The aim of the current study was to perform a systematic review and meta-analysis of data derived from RCTs where CEA and/or CAS had been performed for the treatment of primary atherosclerotic disease, which published surveillance data on rates of restenosis > 70% and/or occlusion, with specific reference to whether untreated asymptomatic restenoses > 70% were associated with a higher risk of late ipsilateral stroke than patients with no significant restenoses. RCTs were chosen (rather than observational studies) because they are prospective, they tend to be conducted with greater scientific rigour, selection bias is reduced because of the randomisation process, and independent observers adjudicate most endpoints.

## MATERIALS AND METHODS

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.<sup>8</sup> PubMed/Medline, Embase, and the Cochrane databases were independently searched by two investigators (R.K., A.B.) from January 1990 until July 2016 to identify RCTs involving CEA and/or CAS. Manual searches were also made of the following journals: *Stroke*, the *European Journal of*

*Vascular and Endovascular Surgery*, the *Journal of Vascular Surgery*, and the *Annals of Vascular Surgery*.

Demographic data retrieved from constituent RCTs included intervention (CEA, CAS), carotid endovascular intervention (CAS, balloon angioplasty, mixed cohort); CEA method (traditional, eversion, mixed cohort), CEA arteriotomy closure (primary, patched, mixed cohort), presence/absence of restenosis > 70% or occlusion, and the mean follow-up period. Studies considered for inclusion in the first meta-analysis (to determine the prevalence of restenosis > 70% or occlusion after CEA and CAS) had to report rates of restenosis > 70% (or occlusion) in the operated ICA during serial surveillance after CEA and/or CAS, but not whether these studies published rates of recurrent ipsilateral stroke.

The second meta-analysis was undertaken to determine whether a restenosis > 70% (or occlusion) after CEA and CAS was associated with higher rates of recurrent ipsilateral stroke. This required the constituent RCTs to report rates of restenosis > 70% and rates of recurrent late ipsilateral stroke. The threshold of 70% was chosen because few surgeons or interventionists would adopt a threshold of > 50% or > 60% for re-intervening in asymptomatic patients, and very few RCTs published outcome data using a stenosis threshold of 80%. Data abstraction was performed independently and the results compared between investigators. If there was any disagreement between the two investigators (R.K., A.B.), this was resolved by consensus discussion or referral to a third party (A.R.N.).

The principal investigators (PIs) of each RCT that were identified for inclusion in the second meta-analysis were contacted for additional information; for example, to clarify ipsilateral stroke rates where these had been combined with late ipsilateral transient ischaemic attack (TIA). All PIs were asked to review their surveillance data in patients with a "restenosis > 70% or occlusion" who suffered a late ipsilateral stroke. This was to determine the severity of the restenosis in the treated ICA in the duplex ultrasound (DUS) surveillance study that immediately preceded stroke onset. In that way, it was possible to determine whether a diagnosis of "restenosis > 70%" (or occlusion) was made before or after stroke onset. Additional data regarding restenosis severity prior to stroke onset were provided from the PIs of eight RCTs, including four with surveillance after different types of patch closure (A.F. AbuRahma, A.R. Naylor) and four RCTs comparing CEA with CAS, including CREST (B.K. Lal), the Endarterectomy Versus Stenting in patients with Severe Symptomatic Stenosis (EVA-3S) trial (J.-L. Mas), the Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial (P. Ringleb), and the Regensburg RCT on CEA versus CAS (M. Steinbauer).

The Jadad score<sup>9</sup> was used to assess the quality of individual RCTs, based on three questions: (i) Was the study described as randomised? (ii) Was the study described as double blind? and (iii) Was there a description of withdrawals and dropouts? To receive a point, the manuscript had to report the number of withdrawals and dropouts in each study group and the underlying reasons. Additional

points were given if the method of randomisation was described in the paper and was deemed appropriate and if the method of blinding was described and considered appropriate. Points were deducted if the method of randomisation was described but deemed inappropriate, and where the method of blinding was described but considered inappropriate. Accordingly, the Jadad score could range from 0 (lowest quality) to 5 (highest quality).

Statistical analyses were performed using the R package for Windows (version 3.0). Random- and fixed effects meta-analyses were performed using the proportions of patients who experienced a restenosis > 70% (or occlusion) as the outcome of interest. Furthermore, the odds ratio (OR) with 95% confidence interval (CI) were calculated for each study to assess the association between restenosis > 70% (or occlusion) and late ipsilateral stroke for the duration of follow-up. Studies where there were no late ipsilateral strokes at all (irrespective of restenosis severity) were excluded from the second meta-analysis. For those RCTs where one subgroup (e.g., no restenosis) reported no recurrent strokes but another subgroup (e.g., restenosis > 70% or occlusion) reported at least one late ipsilateral stroke, a fixed factor of 0.5 was added to cells of the study results with zero strokes to calculate an appropriate odds ratio. This type of continuity correction is a well established approach to incorporate zero-event studies and 0.5 is the commonest choice of correction factor.<sup>10</sup>

ORs were then combined using meta-analysis (fixed and random effects models, where appropriate). Inter study heterogeneity was analysed using the  $I^2$  statistic. This describes the percentage of total variation across studies because of heterogeneity, rather than chance or random error and is a recognised method of quantifying heterogeneity in literature synthesis. An  $I^2$  value greater than 50% reflects significant heterogeneity owing to real differences in study populations, protocols, interventions, and outcomes. Based on the result of the  $I^2$  statistic, a fixed effects model was used to combine studies if  $I^2$  was < 50% and a random effects model if  $I^2$  was  $\geq$  50%. A  $p$  value < .05 was considered to be statistically significant.

## RESULTS

A total of 1562 reports were identified during the preliminary search and a further 327 records identified through other sources. After exclusion of duplicates (common when three large databases are searched), 1306 records were screened and 1253 were excluded (Fig. 1). Fifty-three full text articles were assessed for eligibility, following which 42 were excluded. The main reasons for exclusion were absence of relevant endpoint data (no surveillance undertaken, restenosis > 70% rates not reported separately, no data regarding late ipsilateral stroke) ( $n = 41$ ), the full text was a systematic review or a meta-analysis ( $n = 7$ ), more relevant or greater information was available in a more recent paper by the same authors/study group ( $n = 5$ ), or the full text was not an RCT on reviewing the methodology ( $n = 2$ ). This left 11 RCTs for qualitative and quantitative analyses.<sup>4–7,11–17</sup>

Table 1 details the Jadad score for each RCT, case numbers, number and type of CEA/CAS procedure, Duplex ultrasound (DUS) surveillance strategies for each RCT, DUS criteria for diagnosing > 70% restenosis, studies which reported how many of the cohort were lost to DUS surveillance during follow-up, and whether or not data were provided on late ipsilateral stroke rates and stenosis severity in the surveillance scan prior to stroke onset. The only RCT that did not define DUS criteria for diagnosing restenosis > 70% was SPACE. In this multicentre German/Swiss/Austrian RCT, randomising centres used locally validated DUS criteria.<sup>5</sup> In three RCTs, magnetic resonance angiography (MRA) or digital subtraction angiography were used for corroboration whenever a restenosis > 70% was suspected on DUS.<sup>13,14,17</sup>

### Rates of restenosis > 70% after CEA

Eleven RCTs (4249 patients)<sup>4–7,11–17</sup> reported restenosis rates > 70% or occlusion (Table 2) after any type of CEA (eversion, traditional, patched, primarily closed). Over a mean of 47 months, the prevalence of restenosis > 70% (or occlusion) was 5.8% (95% CI 4.1–8.2). Five RCTs ( $n = 1078$  patients)<sup>12–15,17</sup> reported restenosis rates > 70% or occlusion following patched CEA. Over a mean of 32 months, the prevalence of restenosis > 70% or occlusion was 4.1% (95% CI 2.0–8.4). There were insufficient data to perform a meta-analysis on restenosis > 70% in CEA patients undergoing eversion CEA or primarily closed CEA.

### Rates of restenosis > 70% after CAS or angioplasty

Six RCTs (2916 patients)<sup>4–7,11,16</sup> reported that over a mean follow-up of 60 months, the prevalence of restenosis > 70% (or occlusion) in patients undergoing any sort of endovascular intervention (CAS, balloon angioplasty) was 10.3% (95% CI 6.0–16.4). Five RCTs (2716 patients)<sup>4,5,7,11,16</sup> reported that over a mean follow-up of 62 months, the prevalence of restenosis > 70% or occlusion was 10.0% (95% CI 6.0–16.3) in patients undergoing CAS.

### Restenosis > 70% (or occlusion) and late ipsilateral stroke

**Following CAS.** Four RCTs (Table 3) reported rates of restenosis > 70% (or occlusion) and late ipsilateral stroke in 1964 patients undergoing CAS (i.e., not including balloon angioplasty).<sup>4,5,7,16</sup> Over a mean of 50 months surveillance, one of 125 (0.8%) of CAS patients with a restenosis > 70% (or occlusion) suffered a late ipsilateral stroke, compared with 37 of 1839 (2.0%) of CAS patients who did not have a restenosis > 70%. Using a fixed effects model ( $I^2 = 0\%$ ), the OR was 0.87 (95% CI 0.24–3.21),  $p < .8529$ ,  $I^2 = 0\%$ . The resulting forest plot is detailed in Fig. 2.

If the meta-analysis was restricted to the 1932 patients randomised within the three largest RCTs (CREST, SPACE, EVA-3S<sup>4,5,7</sup>) (Fig. 3), one of 119 (0.8%) patients with a restenosis > 70% or occlusion after CAS suffered a late ipsilateral stroke, compared with 36 of 1813 (2.0%) CAS patients with no restenosis > 70% (OR 0.81; 95% CI 0.19–3.41;  $p = .6845$ ).

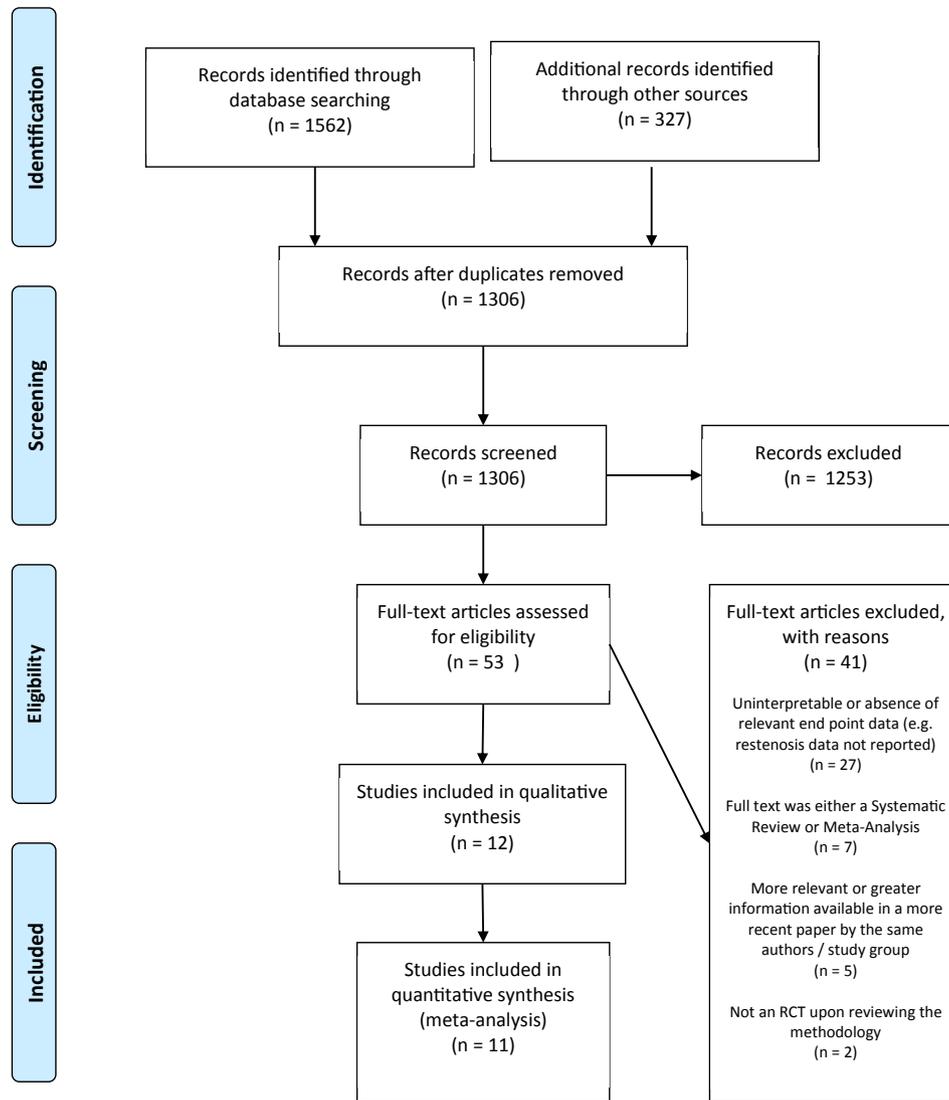


Figure 1. PRISMA flow diagram.

**Following CEA.** Eight RCTs reported rates of restenosis > 70% or occlusion and late ipsilateral stroke in 2839 patients undergoing any type of CEA (eversion/traditional; primary/patched).<sup>4,5,7,13–17</sup> Steinbauer's RCT reported no restenoses/occlusions and no late ipsilateral strokes in 29 CEA patients.<sup>16</sup> Accordingly, the data from this RCT were excluded from the formal meta-analysis. Table 3 and Fig. 4 detail rates of restenosis > 70% or occlusion and whether this was associated with late ipsilateral stroke in the seven remaining RCTs (2810 patients) undergoing any type of CEA (eversion/traditional; primary/patched).<sup>4,5,7,13–15,17</sup> Over a mean of 37 months of surveillance, 13 of 141 (9.2%) CEA patients with a restenosis > 70% or occlusion suffered a late ipsilateral stroke compared with 33 of 2669 (1.2%) patients who did not have a restenosis > 70% or occlusion. Using a fixed effects model ( $I^2 = 0\%$ ), the OR was 9.02 (95% CI 4.70–17.28),  $p < .0001$ ,  $I^2 = 0\%$ .

There were insufficient data to perform meaningful meta-analyses regarding the relationship between restenosis > 70% (or occlusion) and recurrent ipsilateral stroke in

CEA patients undergoing patched repair, primary closure or eversion endarterectomy.

#### **How many CEA patients suffering a late ipsilateral stroke had a restenosis > 70% prior to stroke onset?**

The data in Table 3 and Fig. 4 suggest that the presence of an untreated, asymptomatic restenosis > 70% (or occlusion) was associated with a significant increase in late ipsilateral stroke after CEA. However, the key question is exactly *when* the diagnosis of restenosis > 70% (or occlusion) was made. If it was made after stroke onset, then DUS surveillance could never have prevented them. If the asymptomatic > 70% restenosis was present before stroke onset, then this would support a move towards recommending DUS surveillance and re-intervention after CEA.

Eight RCTs reported 13 late ipsilateral strokes in 141 patients with a restenosis > 70% or occlusion<sup>4,5,7,13–17</sup> (Table 4). The PIs were asked to indicate whether the diagnosis of restenosis > 70% or occlusion was made *after*

**Table 1.** Details of the constituent randomised trials in the various meta-analyses.

Study	Number of CEA/CAS	Jadad score <sup>a</sup>	Mean FU	Surveillance strategy (mo)	US criteria for > 70% restenosis	Lost to DUS FU	Restenosis data + late ipsilateral stroke	Restenosis data prior to stroke onset
CAVATAS <sup>6</sup>	213 CEA any <sup>a</sup> 200 CA + CAS	3	4 y	1, 6 then annually	PSV > 210 cm/s EDV > 110 cm/s ICA/CCA PSV ratio > 4	No data	No	No
ICSS <sup>11</sup>	811 CEA any <sup>a</sup> 752 CAS	3	4.2 y	1, 6, 12 annually	PSV > 210 cm/s EDV > 110 cm/s ICA/CCA PSV ratio > 4	No data	No	No
Mannheim <sup>12</sup>	206 CEA patch 216 CEA primary	4	24 mo	1, 3, 6, 12 annually	PSV > 171 cm/s EDV > 110 cm/s ICA/CCA PSV ratio > 4	No data	No	No
AbuRahma <sup>13</sup>	200 CEA patch	4	26 mo	1 mo + 6 monthly	PSV > 150 cm/s EDV > 90 cm/s <sup>b</sup>	No data	Yes	Yes
AbuRahma <sup>14</sup>	200 CEA patch	4	21 mo	1 mo + 6 monthly	PSV > 150 cm/s EDV > 90 cm/s <sup>b</sup>	No data	Yes	Yes
Naylor <sup>15</sup>	272 CEA patch	4	36 mo	1, 6, 12 mo + annually	PSV > 250 cm/s EDV > 120 cm/s	2	Yes	Yes
CREST <sup>7</sup>	1105 CEA any <sup>a</sup> 1086 CAS	3	24 mo	1, 6, 12, 24, 48 mo	PSV > 300 cm/s	No data	Yes	Yes
SPACE-1 <sup>5</sup>	589 CEA any <sup>a</sup> 607 CAS	3	24 mo	7 d, 1, 6, 12, 24 mo	Local criteria <sup>c</sup>	No data	Yes	Yes
EVA-3S <sup>4</sup>	244 CEA any <sup>a</sup> 239 CAS	3	86 mo	1, 6, 12 mo + annually	PSV > 210 cm/s planimetry	18	Yes	Yes
Steinbauer <sup>16</sup>	29 CEA eversion 32 CAS	3	64 mo	3, 6, 12 mo + annually	PSV < 500 cm/s ICA/CCA PSV ratio 4–8 EDV > 140 cm/s <sup>b</sup>	None	Yes	Yes
Stone <sup>17</sup>	200 patch	4	15 mo	1 mo + 6 monthly	PSV > 274 cm/s	No data	Yes	Yes

CA = carotid angioplasty; CAS = carotid artery stenting; CEA = carotid endarterectomy; ICA = internal carotid artery; mo = months; PSV = Peak systolic velocity; CCA = common carotid artery; EDV = end diastolic velocity; y = years.

<sup>a</sup> Unspecified combination of primarily closed, patched and eversion CEA.

<sup>b</sup> If >70% restenosis suspected, this was corroborated by MR angiography or digital subtraction angiography.

<sup>c</sup> Randomising centres used their own locally validated criteria for diagnosing >70% restenosis or occlusion on duplex ultrasound.

**Table 2.** Meta-analysis of the prevalence of restenosis > 70% in data derived from randomised controlled trials evaluating CEA and CAS.

	No. of RCTs	No. of patients	Mean follow-up (months)	Restenosis > 70% (95% CI)
Any CEA	11 <sup>4–7,11–17</sup>	4249	47	5.8% (4.1–8.2) <sup>a</sup>
Patched CEA	5 <sup>12–15,17</sup>	1078	32	4.1% (2.0–8.4) <sup>a</sup>
CAS or angioplasty	6 <sup>4–7,11,16</sup>	2916	60	10.3% (6.4–16.4) <sup>a</sup>
CAS	5 <sup>4,5,7,11,16</sup>	2716	62	10.0% (6.0–16.3) <sup>a</sup>

CAS = carotid artery stenting; CEA = carotid endarterectomy; RCT = randomised controlled trial.

<sup>a</sup>  $I^2 > 50\%$ ; random effects model used.

**Table 3.** Meta-analysis of the prevalence of late ipsilateral stroke in CEA/CAS patients with and without a restenosis > 70% participating in RCTs.

Procedure	No of RCTs	n	Mean follow-up (months)	Stroke ipsilateral to > 70% restenosis or occlusion	Stroke ipsilateral to restenosis <70%	OR (95% CI)
Any CEA	7 <sup>4,5,7,13–15,17</sup>	2810	37	13/141 9.2%	33/2669 1.2%	9.01 (4.70–17.28) $p < .0001$ , $I^2 = 0\%$ <sup>a</sup>
CAS	4 <sup>4,5,7,16</sup>	1964	50	1/125 0.8%	37/1839 2.0%	0.87 (0.24–3.21) $p = .8339$ , $I^2 = 0\%$ <sup>a</sup>

<sup>a</sup>  $I^2 = 0\%$ ; Fixed effects model utilised.

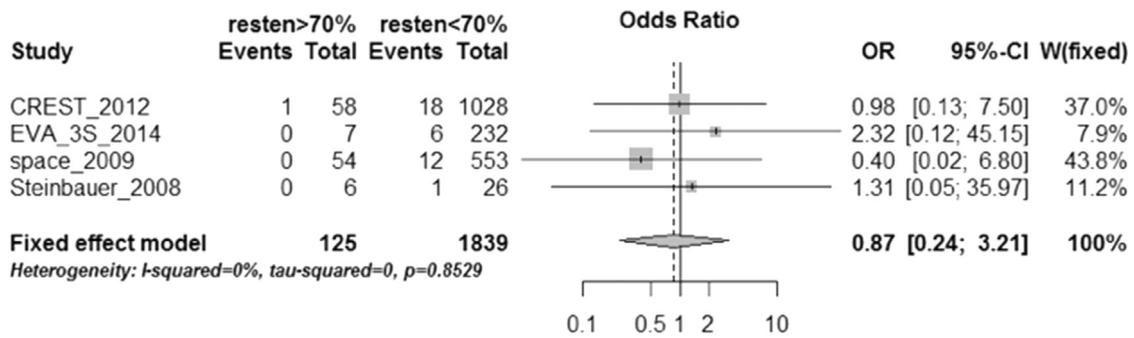


Figure 2. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid artery stenting and the risk of late ipsilateral stroke in all randomised control trials.

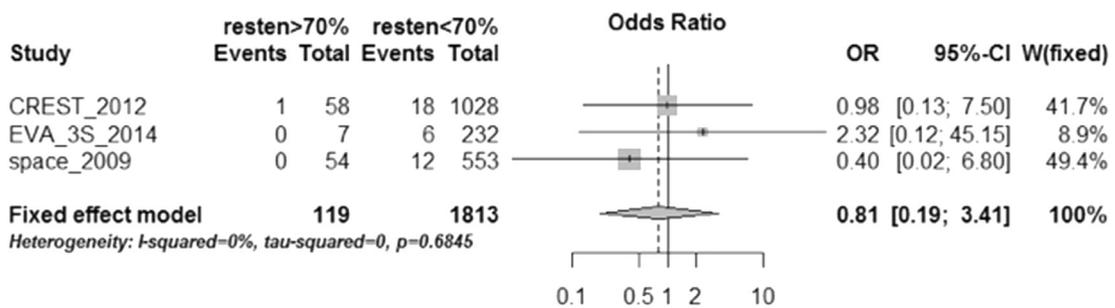


Figure 3. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid artery stenting and the risk of late ipsilateral stroke in CREST, SPACE, and EVA-3S.

stroke onset, or whether it was present at the DUS surveillance scan preceding stroke onset. The findings are detailed in Table 4. In four RCTs,<sup>4,5,13,14</sup> none of the five patients who suffered a late ipsilateral stroke (and who had a restenosis > 70% or occlusion diagnosed at the time of stroke onset) had evidence of a restenosis > 70% (or occlusion) in the DUS scan preceding stroke onset. In the Leicester patch trial, one of two patients destined to suffer a stroke had no evidence of a restenosis > 70% at the DUS

surveillance scan preceding stroke onset.<sup>15</sup> The remaining patient did. Paradoxically, in the latter patient, his stroke followed a CAS procedure that was performed because he had very low middle cerebral artery velocities during carotid clamping (at the original CEA), suggesting that he would not tolerate progression to occlusion. All six CREST patients who suffered a late ipsilateral stroke had an untreated, asymptomatic restenosis > 70% at the DUS surveillance scan preceding stroke onset.

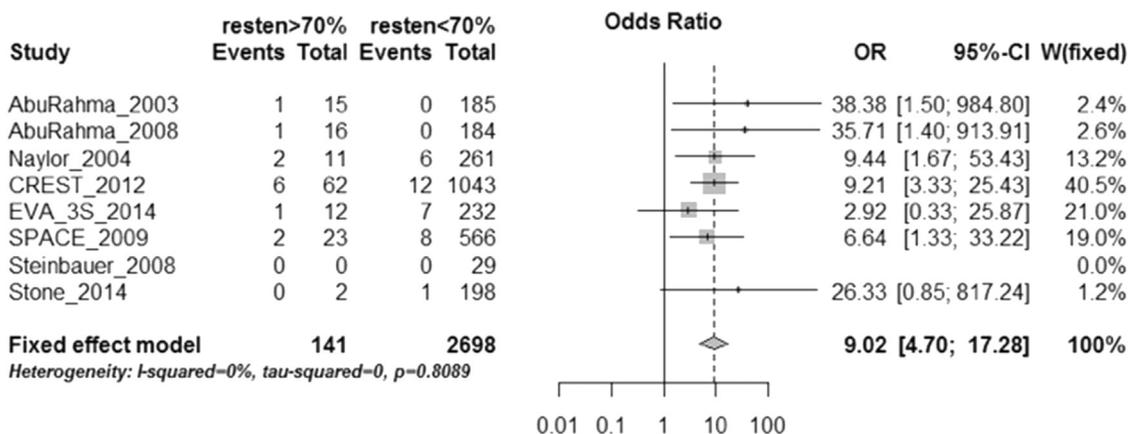


Figure 4. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid endarterectomy and the risk of late ipsilateral stroke all randomised control trials.

**Table 4.** Strokes associated with restenosis >70% or occlusion and whether a restenosis >70% was present on the DUS surveillance scan prior to stroke onset.

Study	n	Restenosis > 70% and ipsilateral stroke as published in RCTs	Restenosis > 70% present on DUS scan prior to stroke onset <sup>a</sup>	Revised stroke risk in patients with untreated > 70% restenosis <sup>b</sup>	Revised stroke risk in patients with restenosis < 70% <sup>b</sup>
AbuRahma <sup>13</sup>	200	1/15	0/1	0/14	1/186
AbuRahma <sup>14</sup>	200	1/16	0/1	0/15	1/185
Naylor <sup>15</sup>	272	2/11	1/2	1/10	7/262
CREST <sup>7</sup>	1105	6/62	6/6	6/62	12/1043
EVA-3S <sup>4</sup>	244	1/12	0/1	0/11	8/233
SPACE <sup>5</sup>	589	2/23	0/2	0/21	10/568
Steinbauer <sup>16</sup>	29	0/0	0/0	0/0	0/29
Stone <sup>17</sup>	200	0/2	0/2	0/2	1/198
Total	2839	13/141 (9.2%)	7/13	7/135 (5.2%)	40/2704 (1.5%)

<sup>a</sup> These additional data were provided by the PIs of the seven RCTs.

<sup>b</sup> Revised calculation of the risk of late ipsilateral stroke in the presence of untreated restenoses > 70% and < 70% after CEA.

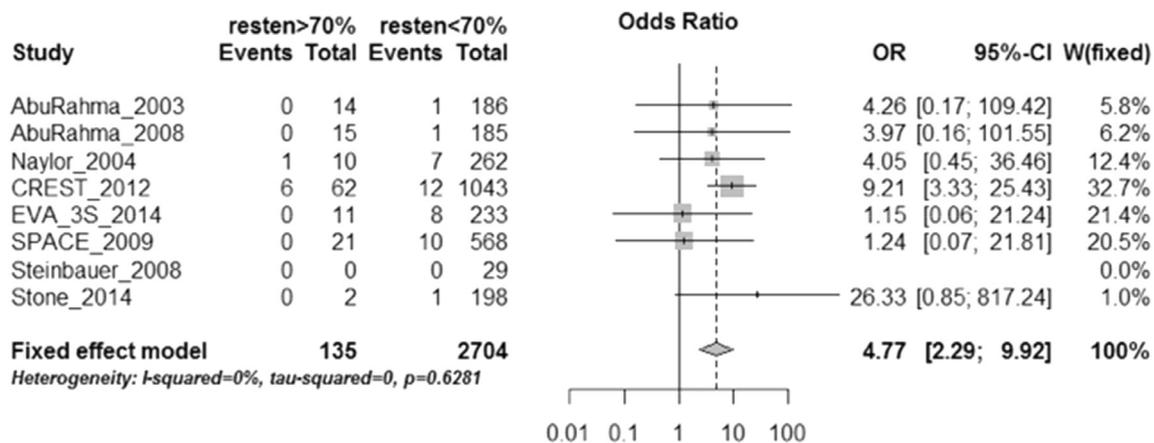
Accordingly, six of the 13 patients (46%) who suffered a late ipsilateral stroke and who were initially reported to have a “restenosis > 70% or occlusion” at stroke onset had no evidence of a restenosis > 70% or occlusion at the DUS scan preceding stroke onset (Table 4); in these six patients, the diagnosis of restenosis > 70% (or occlusion) was made after stroke onset and not beforehand.

Accordingly, seven out of 135 patients (5.2%) with a previously asymptomatic, untreated restenosis > 70% (or occlusion) suffered a late ipsilateral stroke (including 1 asymptomatic patient who suffered their ipsilateral stroke after prophylactic CAS), compared with 40 out 2704 (1.5%) who did not have a restenosis > 70% prior to stroke onset. When these data are factored into a revised meta-analysis (Fig. 5), the presence of an untreated asymptomatic restenosis > 70% was still associated with a significant increase in the risk of late ipsilateral stroke (OR 4.77; 95% CI 2.29–9.92;  $p < .0004$ ). If the previously asymptomatic patient whose ipsilateral stroke followed prophylactic CAS is excluded, six out of 134 (4.5%) with a previously untreated asymptomatic 70–99% restenosis suffered a stroke during follow-up after CEA.

## DISCUSSION

The management of symptomatic and asymptomatic carotid artery disease is one of the most scientifically scrutinised areas of modern vascular practice, aided greatly by the performance of numerous RCTs which have underpinned practice guidelines around the world. However, it is generally accepted that most patients developing a symptomatic 50–99% restenosis following CEA should be considered for re-intervention (unless contraindicated), but there is no consensus regarding the optimal management of asymptomatic 70–99% restenosis.<sup>18</sup>

Restenoses tend to develop in the first 6–12 months after CEA and are usually due to neointimal hyperplasia. Lesions developing after 24–36 months have elapsed tend to represent recurrence of the atherosclerotic process.<sup>19</sup> Several European RCTs comparing CEA with CAS observed no statistically significant association between restenosis > 70% and an increased risk of late ipsilateral stroke.<sup>4–6</sup> However, CREST reported that while a restenosis > 70% after CAS was not associated with an increased risk of late ipsilateral stroke, a restenosis > 70% after CEA was



**Figure 5.** Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid endarterectomy and the risk of late ipsilateral stroke in patients who did (or did not) have an untreated asymptomatic restenosis > 70% or occlusion prior to stroke onset.

associated with a significantly higher risk of late ipsilateral stroke.<sup>7</sup>

Why is this an important issue? No current guideline provides specific advice on how to treat patients with asymptomatic restenoses after CEA. The 2011 14-Society Guidelines suggested that it may be justifiable to undertake redo CEA or CAS in patients with 50–99% stenoses who were symptomatic or whose asymptomatic restenoses became “pre-occlusive”,<sup>2</sup> but this never became a formal recommendation and no-one defined what “pre-occlusive” meant. In a recent meta-analysis, Fokkema et al.<sup>3</sup> observed that two thirds of re-interventions for restenoses were undertaken in patients with asymptomatic lesions, suggesting that many surgeons and interventionists were reluctant not to re-intervene.

The aim of the current systematic review and meta-analysis was to determine whether there was an association between restenosis > 70% (or occlusion) and late ipsilateral stroke. The advantages of using surveillance data from RCTs (as opposed to retrospective, observational studies) was that RCTs are prospective, they tend to be conducted with greater scientific rigour, selection bias is reduced because of the randomisation process, and most endpoints tend to be adjudicated by independent observers.

There were several important findings from the two meta-analyses. First, the overall prevalence of “restenosis > 70%” was relatively low (6% for any type of CEA at 47 months, 4% for patched CEA at 32 months and 10% following CAS at 62 months).

Second, the presence of an asymptomatic restenosis > 70% following CAS did not appear to be associated with an increased risk of late ipsilateral stroke (Table 3, Fig. 2). Over a mean follow-up of 50 months, the prevalence of late ipsilateral stroke was 0.8% in patients with a restenosis > 70% (or occlusion), versus 2.0% in patients with no significant restenosis after CAS. The lack of association with increased stroke risk persisted when only the largest multi-centre RCTs (EVA—3S, SPACE, CREST) were included in the meta-analysis (Fig. 3). Only one ipsilateral stroke was reported in the 125 CAS patients who developed a restenosis > 70% or occlusion during follow-up.

This suggests that few CAS patients with significant asymptomatic restenoses will benefit from routine surveillance and re-intervention, especially as emerging evidence suggests that re-interventions using CAS may confer no additional benefit over non-intervention.<sup>20</sup> This is an important finding, as there has been much debate about how best to diagnose the severity of restenoses after CAS,<sup>21,22</sup> as DUS criteria are quite different to those used to diagnose restenoses after CEA.<sup>23</sup> This is because of the effect of the stented ICA on ultrasound haemodynamics. However, in the absence of clear evidence that restenoses > 70% after CAS are associated with an increased risk of late ipsilateral stroke, the debate about which DUS velocity thresholds should be used to diagnose 70–99% restenoses after CAS becomes less clinically important.

The third important finding was that the presence of a “restenosis > 70%” or occlusion (after CEA) was associated

with a significant increase in the rate of late ipsilateral stroke (OR 9.02; 95% CI 4.70–17.28). Fig. 4 shows that each of the constituent RCTs were reporting broadly similar findings.<sup>4,5,7,13–15,17</sup> However, the key issue to be determined (before advocating a more aggressive approach towards serial surveillance and re-intervention) was to establish exactly when the diagnosis of “restenosis > 70% or occlusion” was made. If the diagnosis was made *before* the patient suffered their ipsilateral stroke, the findings of this meta-analysis assume considerable importance and will influence future guidelines regarding surveillance and treatment strategies for managing restenoses after CEA. If, however, the diagnosis of restenosis > 70% (or occlusion) was made *after* the patient suffered their ipsilateral stroke (i.e., it was not present at the surveillance study preceding stroke onset), the evidence supporting surveillance and re-intervention becomes much less compelling. It has previously been shown in asymptomatic patients with primary atherosclerotic disease who were in serial DUS surveillance, that while disease progression was often associated with onset of TIA or stroke, in at least 50% of cases, the diagnosis of stenosis progression happened at the time of stroke/TIA diagnosis, rather than being evident at the surveillance scan preceding stroke onset.<sup>24</sup> It was important, therefore, to ascertain whether the same phenomenon occurred in patients with asymptomatic restenoses after CEA.

Of the 13 ipsilateral strokes associated with a diagnosis of “restenosis > 70% or occlusion” at the time of stroke onset (Table 4), six (46%) did not have evidence of a restenosis > 70% (or occlusion) at the surveillance scan *prior* to stroke onset (i.e., no DUS surveillance programme could ever have prevented these six strokes). However, after having excluding these six patients, a repeat meta-analysis (Fig. 5) still found that the presence of an untreated, asymptomatic restenosis > 70% after CEA was associated with a significant increase in the risk of late ipsilateral stroke (OR 4.77; 95% CI 2.29–9.92). It is, however, accepted that one of the seven remaining ipsilateral strokes occurred after prophylactic CAS (included on an intention-to-treat basis) and if this patient was excluded, the observed stroke rate would be reduced to six out of 134 (4.5%).

It remains unclear why restenoses > 70% (or occlusion) were relatively commoner after CAS (than CEA), but the likelihood of developing recurrent symptoms appeared to be commoner after CEA. This may be because the mean follow-up in the CAS RCTs was longer than after the CEA RCTs, possibly because four patch RCTs had shorter follow-ups ranging from 21–36 months. It may also be that the lower rate of stroke after CAS may be related to the preferential use of dual antiplatelet therapy after CAS, although most centres only continue dual antiplatelet therapy for 1–3 months post intervention. It may also be that patients destined to develop a significant restenosis (or occlusion) after CEA or CAS were less likely to be taking regular antiplatelet or statin therapy. That information was not available from the constituent studies.

There are, however, a number of important limitations with this meta-analysis. First, is the lack of standardisation

regarding what was considered to be a significant restenosis? A threshold of 70% was chosen as few surgeons or interventionists recommend re-intervening in patients with asymptomatic 50–69% restenoses and few RCTs provided any data on the outcome of patients with untreated restenoses > 80%. Second, were the criteria for making a diagnosis of “restenosis > 70%” after CEA and CAS appropriate? Most were made by DUS (rather than CT or MRA), and ultrasound based criteria for diagnosing a restenosis > 70% differ between CEA and CAS.<sup>21–23</sup> Peak systolic velocity (PSV) criteria for diagnosing an in-stent restenosis > 70% (after CAS) are higher (>300 cm/second)<sup>21,22</sup> than for diagnosing a restenosis > 70% after CEA (274 cm/second<sup>23</sup>), while both are significantly higher than PSV thresholds for diagnosing a 70–99% stenosis in patients with primary atherosclerotic disease (230 cm/second).<sup>25</sup> Table 1 details the various DUS criteria used in the constituent RCTs for diagnosing “restenosis > 70%”. In only one RCT (SPACE) was there no guidance on what criteria should be used. In SPACE, randomising centres were instructed to use locally validated DUS criteria. In three of nine RCTs, anyone suspected of having a “restenosis > 70%” on DUS surveillance underwent corroborative MRA or digital subtraction angiography.<sup>13,14,17</sup> In retrospect, many of the velocity criteria adopted by the RCTs in Table 1 were lower than referenced (above), raising the possibility that some may not have been > 70%. However, even if this were true for CAS patients, it would not change the main message because only one late ipsilateral stroke occurred during follow-up in patients suspected of having a restenosis > 70% during follow-up. Interestingly, if only RCTs where DUS findings were corroborated with MRA or angiography were analysed, zero of 31 patients with an asymptomatic restenosis > 70% after CEA suffered a late ipsilateral stroke,<sup>13,14,17</sup> which would suggest that the true risk of late stroke in patients with corroborated 70–99% restenoses after CEA might be even lower than was observed in this meta-analysis. However, for the purpose of this meta-analysis, it had to be assumed that any diagnosis of “restenosis > 70%” was correct, but it is accepted that this may not always have been the case. Third, other RCTs did not provide additional data regarding restenosis rates and recurrent ipsilateral stroke, despite communications with the various PIs and these studies had to be excluded. Had these been available for inclusion, the meta-analyses would have contained more patients and, therefore, conferred greater power. Fourth, it was not possible to determine whether the method of CEA (eversion vs. traditional) or the mode of arteriotomy closure (primary vs. patched) influenced restenosis rates and late ipsilateral stroke rates, as this was rarely provided as separate data. Most of the large RCTs combined all CEA patients together. Fifth, it may be that the patient’s pre-operative symptom status might have influenced the likelihood of developing a significant restenosis after CEA (e.g., a greater prevalence of restenosis after symptomatic versus asymptomatic carotid interventions) or that plaque echolucency/echogenicity might influence late restenosis

rates.<sup>19</sup> Unfortunately, this information was not available during this meta-analysis. However, because the meta-analysis only involved surveillance data from RCTs, the randomisation process should lessen the risk of selection bias influencing observations.

So what is the clinical relevance of this meta-analysis? There appears to be no compelling evidence that CAS patients will routinely benefit from entering DUS surveillance, as the risk of late ipsilateral stroke is extremely low (<1%) in CAS patients with a restenosis > 70%. In this meta-analysis, 97% of all late ipsilateral strokes in CAS patients occurred in the cohort of 1839 patients who had no evidence of a significant restenosis during follow-up (Table 3).

If the data from Table 2 are extrapolated, about 6% of patients undergoing CEA (of any kind) will develop a restenosis > 70% (or occlusion) over 47 months of follow-up. This means that approximately 1700 CEA patients would need to undergo serial DUS surveillance to identify 100 patients with an asymptomatic restenosis > 70%. Using the revised data from Table 4 (i.e., excluding patients where the diagnosis of restenosis > 70% or occlusion was made after stroke onset), the presence of an untreated, asymptomatic restenosis > 70% would be expected to be associated with a 5% risk of late ipsilateral stroke at 37 months (4.5% if the stroke that followed prophylactic CAS is excluded). If it is assumed that all underwent re-intervention, a maximum of four of five ipsilateral strokes might be prevented at 47 months. However, about 95 of 100 with an asymptomatic restenosis > 70% undergoing redo CEA or CAS would ultimately undergo an unnecessary re-intervention (as they were never destined to suffer a recurrent stroke), but two or three would suffer a peri-operative stroke.<sup>3</sup> In effect, such a strategy could only ever prevent about two or three ipsilateral strokes in the long term. Moreover, despite aggressive DUS surveillance and re-intervening in patients with asymptomatic 70–99% restenoses after CEA, 85% of all late ipsilateral strokes would still occur in the 2704 patients with no evidence of a restenosis > 70% (Table 4).

In summary, this meta-analysis found no evidence that restenoses > 70% after CAS were associated with an increased risk of late ipsilateral stroke, suggesting that routine DUS surveillance offers little benefit to the CAS patient. The presence of a restenosis > 70% after CEA was associated with a significant increase in late ipsilateral stroke, but the actual benefit from re-intervening (in terms of strokes prevented) was small and would not prevent the majority of late ipsilateral strokes from occurring, again casting doubt on the overall benefit of routine DUS surveillance in CEA patients.

#### CONFLICT OF INTEREST

None.

#### FUNDING

None.

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